Research Outcome Goals Excerpted from the February 3, 2003:

Government Performance and Results Act

FY 2004 Final Annual Performance Plan
FY 2003 Revised Final Performance Plan
FY 2002 Annual Performance Report

U.S. Department of Health and Human Services

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NIH GPRA Research Outcome Goals

RISK	1 – 3 years	4 – 6 years	7 –10 years
High	**1a** Conduct medications development with use of animal models, and begin to conduct Phase I and II trials of two potential treatments for alcoholism: cannabinoid antagonist Rimonabant and corticotropin-releasing hormone antagonist Antalarmin. **1b** By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.	**2a** By 2007, demonstrate the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1 diabetes in human clinical studies. **2b** By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans. **2c** Develop methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure. **2d** By 2007, develop an HIV/AIDS vaccine.	**3a** Identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease. **3b** By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens. **3c** Determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease by 2013.
	4a By 2005, develop two new animal models to use in research on at least one agent of bioterror. **4b** By 2005, develop improved animal models that best recapitulate Parkinson's Disease (PD), based emerging scientific findings of genetic or environmental influences, or interactions of genes and the environment on the development of PD.	**5a** By 2007, evaluate the efficacy of three new treatments strategies for HIV infection in phase II/III human clinical trials in an effort to identify drugs that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimen. **5b** Determine the efficacy of statins in preventing progression of atherosclerosis in children with Systemic Lupus Erythematosus (SLE or lupus). **5c** Expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medicines. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs. **5d** By FY 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.	**6a**. Identify the genes that control the risk for the development of age-related macular degeneration and glaucoma in humans. **6b** By 2011, assess the efficacy of at least three new treatment strategies for reducing cardiovascular morbidity/ mortality in patients with type 2 diabetes and/or chronic kidney disease. **6c** By 2012, develop a knowledge base on Chemical Effects in Biological Systems using a "systems toxicology" or toxicogenomics approach.
Low	**7a** By 2005, evaluate 10 commonly used botanicals for inhibition/induction of enzymes that metabolize drugs as a method of identifying potential botanical/drug interactions. **7b** By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarker(s) (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption. **7c** By 2005, create the next generation map of the human genome, a so called "haplotype map" (HapMap), by identifying the patterns of genetic variation across all human chromosomes.	**8a** By 2007, determine the genome sequence of an additional 45 human pathogens and three invertebrate vectors of infectious diseases. **8b** Identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals. **8c** Build a publicly accessible Collection of Reference Sequences to serve as the basis for medical, functional, and diversity studies. A comprehensive Reference Sequence Collection will serve as a foundation for genomic research by providing a centralized, integrated, non-redundant set of sequences, including genomic DNA, transcript (RNA), and proteome (protein product) sequences, integrated with other vital information for all major research organisms. **8d** By 2009, assess the impact of two major Institutional Development Award (IDeA) programs on the development of competitive investigators and their capacities to compete for NIH research funding.	**9a** By 2010, demonstrate through research a capacity to reduce the total years lost to disability (YLDs) in the U.S. by 10 percent by 1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and 2) elucidating the mechanisms by which depression influences at least two comorbid physical illnesses (e.g., heart disease, cancer, Parkinson's disease, or diabetes). Major depression is now the leading cause of YLDs in the nation. **9b** By FY 2010, identify culturally appropriate, effective stroke prevention programs for nationwide implementation in minority communities.

Goals 1a – 9c) NIH GPRA Research Outcome Goals

The research outcome goals that NIH established for fiscal years 1999-2002 under the Government Performance and Results Act (GPRA) were intended to be comprehensive, that is, to encompass the totality of the NIH research portfolio. NIH's approach primarily used qualitative goals and thus relied on the "alternative form" provided under GPRA. Progress toward the qualitative goals was assessed via review of descriptions of science advances, stories of scientific discovery, and significant independent recognition of NIH supported investigators.

Last year, working with OMB and HHS, NIH began revising the comprehensive goals to add greater specificity in terms of desired outcome. Over the course of several meetings among OMB, HHS, and NIH staff, various approaches for articulating NIH research goals and reporting progress were considered. In Summer 2002, NIH developed a new approach to the NIH GPRA research outcome goals. Central to this new approach is a framework that characterizes goals on the basis of risk (likelihood of attaining the goal) and time, fiscal year 2003 and beyond. One way of visualizing this framework is to use a three-by-three matrix (see next page).

In this consolidated GPRA Plan/Report, NIH presents the goals that were developed within the new framework. The goals, a set of specific, representative research aims, were developed based on the following criteria, and are arrayed on the next page in the time/risk matrix.

- **Representative** – The goals will be a sampling of NIH aims that, as a set, represent the NIH mission. NIH has abandoned the previous approach of goals that, collectively, embody the NIH mission comprehensively.
- **Meaningful** - The goals must be credible to the research community, as well as the public and NIH stakeholders.
- **Specific** - Goals should be as specific to a disease or definable problem as possible, with reference to a metric and/or a date for progress/completion, as appropriate.
- **Objective or qualitative** - Objective goals are self-measuring, i.e., they permit a comparison between the actual achievement level and that targeted by the performance goal. If a goal is not self-measuring, i.e., it is qualitative, an independent assessment will have to be conducted in 3-5 years by outside experts.
- **Reportable** - Goals must lend themselves to annual reporting, regardless of whether the goal is objective or qualitative. Reports of incremental progress are fine.
- **Not obviously attainable** - The goal must be recognized as an outcome that *could* be achieved in the future, but may not be reachable for any number of reasons.

To the new goals, NIH is adding the current HIV/AIDS vaccine goal, reformatted to be consistent with the new specific/representative goals. Following presentation of the goals in the matrix format, background statements are provided for each of the goals. Next, NIH will develop plans for annual reporting and assessing performance. Those plans will involve the definition of milestones.

1a - GOAL STATEMENT: Conduct medications development with use of animal models and begin to conduct Phase I and II human trials of two potential treatments for alcoholism: the cannabinoid antagonist Rimonabant and the corticotropin-releasing-hormone antagonist Antalarmin.

***Prevalence/Incidence**:* The 2002 World Health Organization report lists alcohol as the third leading risk factor for preventable, premature death in developed countries, after tobacco and hypertension.[1] In the U.S., alcohol is the third leading root cause of death not attributable strictly to genetic factors, after tobacco and diet/activity patterns.[2] Almost 14 million American adults are alcoholic (physically dependent on alcohol) or abuse alcohol (dysfunctional, but not dependent).[3] Children also are at risk. Almost 30 percent of 9th - 12th graders report having five or more drinks, in a row, at least one day of the previous month.[4]

Disease Burden: Alcohol-use disorders cost U.S. society almost $185 billion each year, through injury, lost wages, property damage, death, and other factors.[5] Unlike other drugs of abuse, alcohol can have toxic effects on any organ in the body. Heavy alcohol use can cause brain damage, contributes to cardiovascular disease, and is a leading cause of liver cirrhosis and pancreatitis.[6] Alcohol is linked to some kinds of cancer.

Rationale: Alcoholism is a chronic disease subject to relapse; sustaining abstinence is the goal of treatment. However, current medications work for some people, but not others. Different factors contribute to abusive drinking and to subtypes of alcoholism. Some alcoholics have a genetic predisposition that affects specific brain systems, such as those regulating stress or rewarding sensations, resulting in molecular and cellular variations. Others are vulnerable to environmental stimuli. Developing more widely effective medications requires (1) understanding the different biological and environmental variations that underlie alcoholism, and targeting them, and (2) a wide array of candidate medications for testing. Animal models enabling us to test compounds in different biological and environmental scenarios are making this goal possible.

Two recently identified classes of compounds with treatment potential are Antalarmin and Rimonabant). By blocking a brain-cell receptor (CRH1) for a hormone that elicits anxiety in response to stress, Antalarmin reduced drinking in monkeys going through alcohol withdrawal. Rimonabant blocks another receptor (CB1) that otherwise would stimulate biological pathways in specific areas of the brain that result in rewarding sensations. In mice, this medication reduced drinking by young animals. We need to continue to cast a wide net to identify compounds with therapeutic potential for the different subtypes of alcoholism. This involves identifying molecular targets and new and existing compounds that act on them, conducting screenings that predict the utility of these compounds, and confirming their utility with animal and human studies.

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[1] World Health Organization. *World Health Report 2002: Reducing Risks, Promoting Healthy Life*. http://www.who.int/whr/en/
[2] McGinnis JM and Foege WH. *Actual Causes of Death in the United States*, JAMA, Nov. 10, 1993, Vol 270, No. 18, p. 2208.
[3] BF Grant et al. *Prevalence of DSM-IV alcohol abuse and dependence -- United States, 1992*. NIAAA's Epidemiologic Bulletin No. 35 18:243-248, 1994.
[4] Centers for Disease Control and Prevention. *Youth 2001*, http://www.cdc.gov/nccdphp/dash/yrbs/2001/youth01online.htm; *Youth Risk Behavior Survey*, CD-ROM Youth '99, and *Youth Risk Behavior Survey*, CD-ROM Youth '97.
[5] Harwood et al. Update of *The economic costs of alcohol and drug abuse in the United States,1992*. NIH Publication No. 98-4327 1-9, 1998. Updated October 1999.
[6] Smart RG and Mann RE. *Alcohol and the epidemiology of liver cirrhosis*. Alcohol Health & Research World 16(3):217-222, 1991.

1b - GOAL STATEMENT: By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.

***Prevalence/Incidence*:** Approximately 20 million Americans are estimated to have sensorineural hearing loss, making this one of the most prevalent disabling conditions in the United States. Hearing loss can be hereditary, or it can result from disease, trauma, or long-term exposure to damaging noise or medications. The condition can vary from a mild but important loss of sensitivity, to a total loss of hearing.

Disease Burden: Sensorineural hearing loss affects people of all ages, in all segments of the population, and across all socioeconomic levels. It can harm an individual's physical, cognitive, behavioral, and social function and is caused by a problem in the cochlea or the auditory nerve; parts of the ear that help sound impulses reach the brain. Hearing aids are the main form of treatment for this condition, however only 20 percent of those who could benefit from hearing aids actually use them.[1]

Rationale: A hearing aid is a battery-operated device that amplifies and changes sound to allow for improved communication. Hearing aids receive sound through a microphone, which then converts the sound waves to electrical signals. The amplifier increases the loudness of the signals and then sends the sound to the ear through a speaker. A vast array of hearing aid technology is available, ranging from simple and relatively inexpensive analog circuits to complex and expensive digital devices that require sophisticated fitting procedures.

Although hearing aid technology has advanced rapidly over the last few decades with the development of microelectronic components, the various hearing aids currently available still do not function well when sound from more than one source is present. Most hearing aids are designed for compensating for high-frequency hearing loss and for suppressing static noise in a room. However, hearing aids are not particularly effective in restoring the listener's ability to sort a single speech sound among competing sources (as in meetings, banquets and sporting events).

NIH-supported scientists have been studying a tiny fly, *Ormia ochracea*, with such acute directional hearing that it has inspired ideas for a new generation of hearing aids. The biological lessons provided by this fly's abilities in hyper acute time coding and localization of sound provide strategies for improved nano/micro-scale directional microphones in hearing aids that would focus sound amplification on speech. Applications of these new principles may improve the quality of life for individuals with hearing loss who depend upon hearing aids to understand spoken language.

[1] Larson V, et al: Efficacy of 3 Commonly Used Hearing Aid Circuits. JAMA 248: 1806-1813, 2000.

2a - GOAL STATEMENT: By 2007, demonstrate the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1 diabetes in human clinical studies.

***Prevalence/Incidence*:** Type 1 diabetes is an autoimmune disease in which the immune system attacks and destroys the insulin-producing islet cells of the pancreas.

- ~300,000-500,000 Americans have type 1 diabetes; ~120,000 are <20 years of age, making this one of the most common chronic diseases of childhood.[1]
- ~30,000 new cases occur each year, the majority with onset in early childhood and teens; ~1 in 300 cases of diabetes with onset in adulthood is autoimmune in origin.[2]

Disease Burden: Type 1 diabetes is a chronic, life-long disease characterized by elevations in blood sugar that, over time, lead to severe and life-threatening complications, including: heart disease; blindness; peripheral neuropathy; foot ulcers; and kidney failure. Treatment requires insulin administration through multiple daily insulin injections or use of an insulin pump and careful attention to diet and activity; blood sugar levels must be measured several times a day by finger pricks. However, even with careful attention to insulin dosing, even the most medically compliant patients are rarely able to maintain "tight" or physiologic control of their blood sugar. As a result, existing treatments can delay and diminish, but not prevent, many of the complications of diabetes. Even with careful attention to control of blood sugar, type 1 diabetes results in a reduction in quality of life and shortens life-span by ~15 years.

Rationale: Whole pancreas and pancreatic islet transplants offers type 1 diabetics the potential for physiologic control of blood sugar as an alternative to insulin therapy. Whole pancreas transplantation is a technically difficult procedure, while pancreatic islet cell transplantation is a minimally invasive procedure. In islet transplantation, cells from the pancreas called "islets" are isolated from a donor pancreas and injected into a large blood vessel that supplies the liver. The transplanted islets lodge in the liver where they produce insulin. Until recently, the intermediate and long-term success of this procedure has been disappointing: of the more than 300 islet transplants performed over a decade, fewer than 10% remained insulin-independent one year after the procedure. However, recent advances in pancreatic islet cell preparation and improvements in immunosuppressive regimens that are required to prevent transplant rejection have dramatically improved the outcome of islet transplantation. As a result, approximately 70-80% of type 1 diabetics can be expected to remain insulin-independent two years following islet transplantation. Despite these advances, patients must remain on potent immunosuppressive drugs to prevent immune-mediated rejection of the transplanted islet cells. Immunosuppressive agents may increase the risk of serious infection and other complications, such as hypertension and cardiovascular disease.

The successful induction of immune tolerance is a major therapeutic goal for the treatment of many immune-mediated diseases, including autoimmune disorders such as type 1 diabetes. Research is underway to develop selective, short-term and durable therapies that will eliminate the pathogenic immune responses, such as graft rejection and autoimmune injury, while preserving protective immunity. Tolerance induction holds great potential for improving the quality of life for those individuals afflicted by type 1 diabetes and other immune-mediated diseases. If successful, tolerance induction would: 1) enable life-long rejection-free maintenance of islet cells; and 2) eliminate ongoing autoimmune injury to transplanted islets without the many adverse effects of broadly immunosuppressive drugs.

[1] Diabetes in America, 2nd edition, 1995; NIH publication No. 95-1468, page 1.
[2] Diabetes in America, 2nd edition, 1995; NIH publication No. 95-1468, page 40.

2b - GOAL STATEMENT: By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.

Prevalence: The number of overweight and obese Americans has risen dramatically in the past two decades and is now at epidemic levels.

- Over 60 percent of adults are overweight; of these, approximately 31 percent are obese.[1]
- About 15 percent of children and teens ages 6-19 are overweight,[2] with ominous implications for our Nation's future health.
- Racial and ethnic minority populations are disproportionately affected by obesity, particularly African American, Hispanic, and Native American women and children.

Disease Burden: Obesity is associated with numerous serious diseases, including type 2 diabetes, heart disease, stroke, osteoarthritis, gallstones, breathing problems, and cancer. Type 2 diabetes, formerly viewed as a disease of adults, has been increasingly reported in children. This alarming trend is thought to be a consequence of increased obesity along with decreased physical activity. In addition to the negative impact on quality of life and the increased risk of premature death, overweight and obesity exact enormous economic costs. In 2000, costs associated with obesity were estimated to be $117 billion.[3]

Rationale: Overweight and obesity develop when energy intake (food calories) exceeds energy expenditure. While genetic factors may contribute substantially to the predisposition towards obesity, the recent dramatic increase in obesity prevalence is clearly fueled by environmental and behavioral changes interacting with genetic susceptibility. Results from the NIH-funded Diabetes Prevention Program clinical trial demonstrated a substantially reduced incidence of type 2 diabetes in a high risk population using an intervention that combined moderate weight loss and exercise; however, these modest lifestyle changes required intensive individual behavioral intervention. Thus, the goal of obesity prevention may benefit greatly from new approaches to modify factors pervasive in the environment that promote over-consumption of food and sedentary lifestyles, complemented by further research on strategies to help individuals achieve and maintain behavior changes. For people who are extremely obese, expected weight loss from behavior change alone may not be sufficient to have a major impact on health. Bariatric surgical procedures that restrict stomach size are being increasingly performed to treat severe obesity and can have dramatic benefits, but also carry substantial risks. Accelerated clinical research on this surgery will enhance patient evaluation, selection, and follow-up care. Finally, the continued elucidation of the molecular factors and pathways responsible for appetite regulation, metabolism, and energy storage offers rich prospects for the development of new drugs that will promote safe and effective long-term weight loss. A major goal of NIH-funded research is to develop and evaluate strategies to prevent obesity and to promote sustained weight loss in individuals who are overweight or obese. In addition to mechanisms falling within the three broad approaches to weight regulation just described, evaluation of other as yet unknown strategies may also be necessary in order to achieve success in meeting the goal. If successful, the approaches would decrease risk for the life-threatening diseases that accompany excess weight and would also reduce the social and economic costs of obesity.

[1] Flegal et al., *JAMA* 288: 1723-7, 2002.
[2] Ogden et al., *JAMA* 288: 1728-32, 2002.
[3] The Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity, 2001, p. 10.

2c - GOAL STATEMENT: Develop methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.

Background: Classification of domains by computational sequence analysis is a powerful means to deduce the function of newly discovered proteins. In the context of proteins associated with human disease, this analysis can generate hypotheses concerning the metabolic pathways in which the proteins act and greatly accelerate research into the molecular basis of disease and therapy. Domain analysis identifies regions of high sequence similarity with respect to other proteins from a variety of organisms. Conserved domains, as these regions are called, have been shown to be fundamental units of biological function; they adopt similar 3-dimensional structures and interact with other molecular components of living cells in similar ways. A comprehensive domain database, searchable over the internet, will therefore be a powerful research tool for academic and industrial scientists with diverse interests.

Rationale: A comprehensive database is achievable because proteins contain only a few thousand domain families. Maintaining a collection up to date with respect to current knowledge nonetheless represents a challenge that can be met only by development of new methods for large-scale comparative analysis of molecular data, which allow curators to focus on functional annotation. The continuing investment of Federal agencies and other organizations in genome sequencing and structural genomics will yield the greatest return when combined with efforts to organize this data in useful ways. The conserved domain database anticipated here represents an advance over previous efforts because it will apply structure-based alignment and molecular evolutionary classification in a systematic and ongoing manner.

This resource will be particularly valuable to researchers such as medicinal chemists who require a synthesis of information on protein biological function, 3-dimensional structure, and sequence conservation. Effective anti-viral drugs have been designed by targeting the conserved regions of viral proteins, for example; the virus is unable to develop resistance to these drugs because sequence changes that block drug binding also block the normal function of the protein. By describing conserved regions in detail, the resource proposed here provides information that is directly useful to the medicinal chemist undertaking this research.

2d - GOAL STATEMENT: By 2007, develop a HIV/AIDS vaccine.

Incidence/Prevalence: Globally, over 40 million people (37.1 million adults and 3 million children) were living with AIDS at the end of 2001. In 2001, 3 million people died from AIDS, and 5 million people were newly infected with HIV. Of the 5 million new infections, 800,000 were in children. More than 95 percent of new HIV infections occur in the developing world, with 70 percent occurring in sub-Saharan Africa and 20 percent in Asia and the Pacific. Most of these new infections are in young adults, with an increasing number among women. In the United States, close to 950,000 people are living with HIV/AIDS, and each year 40,000 new infections occur, of which more than one-half are in individuals younger than 25 years of age.[1,2]

Disease Burden: AIDS is caused by the human immunodeficiency virus. Infection with the virus leads to destruction of a person's immune system, making the victim highly susceptible to multiple infections and certain cancers. AIDS is a fatal disorder.

Rationale: Significant progress has been made in HIV/AIDS research since 1981 when AIDS first emerged as a global infectious disease. Research has led to a better understanding of the structure of HIV and how HIV attacks the immune system, and the role of the immune system in controlling HIV infection. Potent therapeutic regimens commonly referred to as HAART, have been successful in suppressing HIV to virtually undetectable levels in the blood and in decreasing the incidence of opportunistic infections. HAART has greatly improved the quality of life of many HIV-infected individuals and has led to a dramatic decline in HIV-infected people in the United States. Educational and counseling efforts have had some success and remain essential, however, it has become evident that these prevention activities alone are not sufficient to contain the spread of the disease. Despite these advances, the HIV pandemic continues to rage around the world.

The development of a safe and effective vaccine against HIV is critical to worldwide efforts to control HIV/AIDS, and offers the best hope for halting the HIV/AIDS pandemic. An HIV vaccine that is simple to administer, inexpensive, and induces long-lasting immunity against most HIV sub-types is the ideal prevention strategy.

Since the beginning of the epidemic, NIH's comprehensive research program has made significant progress in elucidating the structure of HIV and how HIV attacks the immune system, understanding the role of the immune system in controlling HIV, developing new and improved models for testing candidate vaccines, and in sponsoring and conducting clinical trials. NIH's HIV vaccine program supports research on novel vaccine concepts, genetic and immunologic variation, mucosal immunity, delivery methods, adjuvants, and correlates of immune protection. At the preclinical level, NIH's programs include support for the development of new candidate vaccine designs, evaluation in non-human primate models of HIV/AIDS, pilot-lot production of new candidate vaccines, and additional preclinical work required for the advancement into human trials. At the clinical level, the program coordinates all phases of clinical trials of candidate HIV vaccines and supports work to characterize potentially protective immune responses in vaccinated volunteers.

[1] CDC, HIV/AIDS Surveillance Report, 13 (No. 2):1-44, 2001
[2] UNAIDS Report on the Global HIV/AIDS Epidemic, December 2001

3a - GOAL STATEMENT: Identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease.

Prevalence/Incidence: Alzheimer's disease (AD) is a progressive, at present irreversible, brain disease that slowly destroys memory and thinking skills, eventually even the ability to carry out the simplest tasks of daily living.

- A consensus statement developed by the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society estimates the number of AD cases at 4 million nationally, and still concludes that Alzheimer's disease and related dementias are under diagnosed.[1]
- The prevalence of the disease doubles each 5 years over the age of 65.
- It is estimated that the prevalence of AD will nearly quadruple in the next 50 years.[2]

Disease Burden: The cost of AD care appears to vary by the stage of the disease. In 1996, annual costs of caring for patients with mild, moderate, and severe Alzheimer's disease were $18,408, $30,096, and $36,132, respectively.[1] The national cost of caring for people with AD is now thought to be about $100 billion every year.[2]

Rationale: In 1999, at the direction of Congress, the National Institute on Aging (NIA), in conjunction with the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Mental Health (NIMH), and the National Institute of Nursing Research (NINR) embarked on the Alzheimer's Disease Prevention Initiative. A major focus of this initiative is on accelerating movement of promising new treatments and prevention strategies into clinical trials.

Advances in genetic, molecular and epidemiological research have increased our understanding of the biologic processes involved in the onset and progression of AD and provided important opportunities to test promising new interventions. Clinical research is rapidly developing ways of identifying persons early in the course of AD and better ways of predicting and following the progression of the disease. Ongoing clinical trials and those in the planning stages are focusing on specific biologic processes including inflammation, free radical accumulation, amyloid deposition, and cell death that scientists believe are among the first changes to appear in the brains of patients with AD. Completing these long-term human trials will identify ways that specific drugs can be used to most safely and effectively intervene in order to delay the progression, delay the onset, or prevent Alzheimer's disease.

[1] Small, GW et al. *JAMA* 16: 1363-1371, 1997.
[2] Brookmeyer, R, et al. *American Journal of Public Health* 88: 1337-1342,1998.
[1] Leon J, et al. *Health Affairs* 17(6): 206-216, 1998.
[2] Ernst, RL, et al.. *Arch Neurol* 54: 687-693, 1997.

3b - GOAL STATEMENT: By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens.

Background: In the 1940's, the widespread availability of newly discovered antibiotics led to a dramatic reduction in illness and death from infectious diseases. However, bacteria and other disease-causing organisms are remarkably resilient and have developed mechanisms of resistance that thwart or block the action of antimicrobial drugs. Microbes that were once easily controlled by antimicrobial drugs are causing infections that no longer respond to treatment with these drugs. In addition, new, frightening, and unforeseen infectious disease threats have emerged, including threats posed by agents of bioterrorism. The threat of these infectious agents coupled with the emergence of antimicrobial resistance is a grim and foreboding reminder of the power, destructiveness, and endless adaptability of infectious microbes and the global importance of research to treat these infections. A "universal antibiotic," a drug effective against a wide spectrum of infectious diseases, would help address these challenges.

Rationale: The U.S. government's ability to detect and counter a biological attack requires basic research aimed at understanding both the organisms that might be used as agents of bioterrorism and how the human immune system responds to those organisms. The National Institute of Allergy and Infectious Diseases (NIAID) has developed a comprehensive strategic plan and detailed research agendas (http://www.niaid.nih.gov/dmid/bioterrorism/) for the Category A, B, and C biological pathogens considered by the CDC to be the most serious bioterror threats.

Several of these pathogens are bacteria that can persist and grow within host cells and present unique challenges to biodefense researchers. The recent NIAID Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research on the Category B/C Agents stressed the need for more research on intracellular bacterial infections (infections within the cell) and approaches to their treatment and prevention. The bacterial mechanisms required for intracellular survival and the cellular changes induced in response to infection remain poorly understood. Therefore, characterizing the genetic and biochemical requirements of intracellular infections could lead to new therapeutic targets such as one universal antibiotic effective against multiple classes of bacterial/biological pathogens.

NIH scientists are working to decipher the basic mechanisms of non-specific (or innate) host defense against microbes. Understanding the molecular events that constitute the generic immune response to microbes that are "new" to the immune system, that is, those previously unseen via vaccination or prior infection, is key to the development of novel therapeutics that will be effective against multiple pathogens.

3c - GOAL STATEMENT: Determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease by 2013.

***Background**:* For many serious health conditions, early detection offers the best hope for cure. However, many individuals obtain a correct diagnosis only after they experience symptoms--and then it may be too late. The composition of saliva and other oral fluids reflects serum levels of substances that may be useful for diagnostic applications—such as therapeutic and recreational drugs, hormones, immunoglobulins, and toxic molecules. Oral fluids can also be used as a source of host or pathogen DNA. Thus, oral fluids could potentially be used to assess and monitor systemic health and disease, as well as determine exposure to environmental and occupational hazards. Real-time monitoring of oral fluids may also have a role in biodefense by facilitating early detection of agents used in bioterrorism.

Rationale: Saliva is easy to collect, and poses none of the risk, fears, or "invasiveness" concerns occasioned by blood tests or urine sampling. Miniaturization of the "lab on a chip" may allow placement of the detection device directly in the mouth, making sample collection unnecessary. However, because oral levels of most analytes are lower than blood levels, sensitive analytical techniques are required. (Analytes are any substance or chemical constituent of a body fluid that is analyzed.) To overcome this challenge and demonstrate the feasibility of salivary diagnostic tools, the NIH is taking steps to accelerate the technology needed to analyze oral fluids. This effort will require highly sensitive and accurate methods for the rapid detection of informative analytes in saliva, thus indicating the early stages of emerging disease. Our goal is to determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease by 2013. However, if successful, this line of research could yield improved detection for a number of diseases, as well as dramatically reducing the cost and risk associated with blood test based diagnostics. This would catalyze a shift of our current system of disease detection to one of health surveillance within the community or home.

4a - GOAL STATEMENT: By 2005, develop two new animal models to use in research on at least one agent of bioterror.

Background: Deliberate exposure of the civilian population of the United States to *Bacillus anthracis* (anthrax) spores revealed a gap in the nation's overall preparedness against bioterrorism. These attacks uncovered a need for tests to rapidly diagnose, vaccines and immunotherapies to prevent, and drugs and biologics to cure disease caused by agents of bioterrorism. The lack of routine clinical importance, and thus the absence of scientific and clinical expertise associated with a microbe, is a hallmark of a successful bioterrorist agent. The development of centralized sources of generalized as well as specific expertise in bioterrorism areas will be required to speed the development of new generation products. The NIAID Strategic Plan for Biodefense Research offers more detailed information on the types of biodefense research supported by NIH, including specific goals for each research category.

Rationale: New products and ideas must be thoroughly tested in the laboratory to ensure that they are safe and that they work. For example, scientists conduct tests in artificial environments (*in vitro*) and in animals when they develop and test vaccines, therapeutics, and diagnostics. In addition, safety testing in the lab is required to speed the development of new generation products. *In vitro* and animal models provide information that can be used to move the processes that occur in the laboratory to humans. In the field of biodefense research, animal models will be critical to FDA approval of therapies and vaccines, since, in most cases, clinical trials in humans to test efficacy are not possible or ethical. A number of promising candidate therapies and vaccines have been identified for bioterrorism organisms/diseases. However, development has been delayed because of the lack of standardized animal models in which to evaluate these candidates. New models need to be developed, particularly for non-human primates. The development of many infectious diseases and the response to therapy in non-human primates are similar to the human response (the rhesus macaque, a type of monkey, is particularly useful in medical research). However, the use of non-human primates is limited by their cost and difficulty in acquiring and maintaining them. The shortage of rhesus macaques is severely limiting development of new vaccines and therapies. Given the current level of interest in developing additional therapeutic and prevention strategies, particularly for organisms with potential use in bioterrorism, NIH must expand current resources, including animal models that are not based on non-human primates, for therapeutics and vaccine development.

In addition, NIH's biodefense and emerging infectious diseases research opportunities include support for developing animal models to: understand disease-causing mechanisms and pathogen/host interactions; define the body's natural and learned protective immune mechanisms, and study vaccines, diagnosis and treatment regimens for pathogens; define how these infections impact the immune system; determine the ways that these infections have adapted to avoid detection by immune cells; and study mechanisms of vaccination adverse events, including those in at-risk populations, methods for avoiding the introduction of adventitious agents during vaccine manufacture, and novel methods of vaccine production to enhance vaccine safety.

4b - GOAL STATEMENT: By 2005, develop improved animal models that best recapitulate Parkinson's disease (PD), based on emerging scientific findings of genetic or environmental influences, or interactions of genes and the environment on the development of PD.

Prevalence/Incidence: PD is a neurodegenerative disease for which there is no known cure.

- Incidence: 50,000 cases per year[1], increases dramatically after age 50
- Prevalence: estimates range from 500,000[1] to 1 million individuals in the U.S.[2]

Disease Burden: Parkinson's disease is a devastating, progressive motor disorder, characterized by rigidity, poor balance, and uncontrollable shaking or tremors; those affected by PD eventually lose their independence. PD is marked by a loss of neurons that produce the neurotransmitter dopamine, which are an essential part of the brain pathways controlling purposeful movement. The total economic cost per year was estimated to be $6 billion in 1992.[3] Most individuals with PD are treated with pharmacologic agents that mimic the actions of the lost dopamine. Although these drugs provide symptomatic relief, they do not cure or slow disease progression, are of limited benefit in later stages of the disease, and can produce undesirable side effects.

Rationale: In order to facilitate the understanding and treatment of any human disease, it is desirable to create animal models that precisely recapitulate the disease process, including pathways of disease causation and the impact of the disease on cellular processes, organ function, and ultimately, behavior. With such models in hand, researchers could track the earliest molecular events in the disease and develop intervention strategies to delay, or even prevent its progression. In the case of PD, researchers would *ideally* like to have access to an inexpensive, reproducible animal model that captures both the genetic and environmental roles in causation; reproduces the cellular changes that occur in PD over an appropriate period of time; and leads to behaviors in the animal that approximate the effects of the disease on humans.

Over the years, the research community has developed several animal models of PD that have been instrumental in accelerating our understanding of the disease process[4]. One such model is produced through the exposure of primates to MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), a chemical substance with structural similarities to some pesticides. Although this model is likely to remain useful for predicting therapeutic efficacy, it is costly, and does not reproduce some key features of PD (e.g., the progressive nature of the disease, some cellular features of affected neurons, and the combined effects of the environment and genes on disease causation). By contrast, non-primate models have offered important practical benefits for dissecting gene-environment interactions in PD. For example, the creation of mice and fruit flies expressing mutant forms of a gene (alpha-synuclein) implicated in PD have provided an opportunity for studying the effects of environmental agents on key genes and proteins involved in the disease process. Further, the recent discovery that pesticide exposures (e.g., rotenone) can produce parkinson-like effects on neurons and behavior in rodents offers another possible strategy for understanding the effects of the environment on this disease.

Together, these models have enabled researchers to learn a great deal about the neural systems that are affected by PD, the molecules within cells that may play a role in the disease process, and the potential for various therapies to treat the disorder. However, each has its merits and limitations, and an optimal model is still not available to the PD research community[5]. For this reason, a collaborative effort will be

[1] NIH Cost of Illness Report, 2000, p. 98.
[2] Herndon, CM, et al. Parkinson's disease revisited. J. Neurosci. Nurs. 2000; 32(4): 216-221.
[3] NIH Cost of Illness Report, 2000, p. 98.
[4] Greenamyre JT, Animal models of Parkinson's disease. Bioessays 2002 Apr;24(4):308-18
[5] Beal, MF, Experimental models of Parkinson's disease. Nature Reviews Neuroscience. 2001; 2: 325-332.

needed in the future to capitalize on findings related to environmental and genetic influences on PD, and to develop this knowledge into inexpensive, reproducible animal models of PD that simulate the disease process even more accurately than do the models that are currently available, and improve our ability to test therapies.

5a - GOAL STATEMENT: By 2007, evaluate the efficacy of three new treatments strategies for HIV infection in phase II/III human clinical trials in an effort to identify drugs that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimen.

Prevalence/Incidence: Globally, over 40 million people (37.1 million adults and 3 million children) were living with AIDS at the end of 2001. In 2001, 3 million people died from AIDS, and 5 million people were newly infected with HIV. Of the 5 million new infections, 800,000 were in children. More than 95 percent of new HIV infections occur in the developing world, with 70 percent occurring in sub-Saharan Africa and 20 percent in Asia and the Pacific. Most of these new infections are in young adults, with an increasing number among women. In the United States, close to 950,000 people are living with HIV/AIDS, and each year 40,000 new infections occur, of which more than one-half are in individuals younger than 25 years of age.[1,2]

Disease Burden: AIDS is caused by the human immunodeficiency virus. Infection with the virus leads to destruction of a person's immune system, making the victim highly susceptible to multiple infections and certain cancers. AIDS is a fatal disorder.

Rationale: Over the past 13 years, efforts to develop drugs to treat HIV infection and/or AIDS have mainly concentrated on developing inhibitors of two important enzymes in the lifecycle of the virus, namely reverse transcriptase (RT) and protease (PR). When used in combination, RT and PR inhibitors (known as highly active antiretroviral therapy, or HAART) have been successful in decreasing the amount of HIV in the blood of many infected individuals to undetectable levels, decreasing the incidence of opportunistic infections and decreasing the number of AIDS-related deaths in the developed world. Nonetheless, complications have emerged with the use of these drugs, including the development of drug resistance, metabolic abnormalities and toxicities, and noncompliance due to the complexity of these regimens. Moreover, damage to the immune system is only partially repaired by currently available antiretroviral therapy. Thus, there remains an urgent need for the discovery and development of new classes of antiviral drugs for the treatment of HIV infection and AIDS that are not only less toxic and simple to use, but that are affordable and available for worldwide use.

Recently, research has identified several new classes of potential drugs to treat HIV infection which are in the early stages of development. Examples of these new classes of drugs include agents that interfere with other stages of the virus lifecycle, such as the initial attachment of the virus to the host cell and the entry of the virus into the cell. Another example includes drugs that interfere with other key steps in the virus' lifecycle, such as when HIV uses its integrase enzyme to insert its own genetic material into a host cell's DNA. Both entry inhibitors and inhibition of HIV integrase are attractive therapeutic strategies, since both would potentially protect healthy cells from infection, thereby helping to bolster the immune system. Further, there may be significant synergy when these agents are used in combination. NIH will continue to support the basic, preclinical and clinical development of novel therapeutics, including the identification of new host and viral targets, novel drugs and delivery systems, and immunological approaches to address the dual problems of drug resistance and toxicity. In addition to new therapeutic agents, there is a need to develop and test therapeutic vaccines for HIV/AIDS. The goal of a therapeutic vaccine is to enhance the ability of the immune system to fight HIV infection and prevent or delay the onset of AIDS (in contrast to a vaccine which prevents HIV infection). Since there are known and well defined immune defects caused by HIV, it might be possible to design vaccines, which in conjunction with HAART, can rebuild the immune system and establish a fully efficient host immune response that controls the virus. These types of strategies would have a profound impact domestically as well as in the developing world.

[1,2] CDC, HIV/AIDS Surveillance Report, 13 (no. 2):1-44, 2001 UNAIDS Report on the Global HIV/AIDS Epidemic, December 2001

5b - GOAL STATEMENT: Determine the efficacy of statins in preventing progression of atherosclerosis in children with Systemic Lupus Erythematosus (SLE or lupus).

Prevalence/incidence: It is difficult to estimate how many children in the United States have lupus because its symptoms vary widely and its onset is often hard to pinpoint. Lupus is three times more common in African American women than in Caucasian women and is also more common in women of Hispanic, Asian, and Native American descent.[1]

***Disease Burden*:** Lupus is a disorder of the immune system known as an autoimmune disease. In autoimmune diseases, the body harms its own healthy cells and tissues, leading to inflammation and damage to various body tissues. Lupus can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. Although people with the disease may have many different symptoms, some of the most common ones include extreme fatigue, painful or swollen joints (arthritis), unexplained fever, skin rashes, and kidney problems.

Lupus is a complex disease whose cause is unknown. It is likely that there is no single cause but rather a combination of genetic, environmental, and possibly hormonal factors that work together to cause the disease. Scientists are making progress in understanding the processes leading to lupus. Age at disease onset is a predictor of outcome, and children often have severe end organ disease. At present, there is no cure for lupus. Lupus is the focus of intense research as scientists try to determine what causes the disease and how it can be best treated.

***Rationale*:** Atherosclerosis is a thickening of the inside walls of arteries that is caused by the gradual buildup of fatty substances in arteries. This thickening narrows the space through which blood can flow, and can result in heart attacks or strokes. Atherosclerosis usually occurs when a person has high levels of cholesterol (a fat-like substance), which can build up on the walls of arteries. We know that women with lupus have a significantly increased risk for cardiovascular complications related to premature atherosclerosis, and children do as well. The data on cardiovascular and lipid abnormalities in children with lupus implicate atherosclerosis as an important potential source of long-term morbidity and mortality. Statins are drugs that lower cholesterol in blood and decrease the risk for atherosclerosis and cardiovascular disease. Not only do statins decrease mortality and morbidity from coronary artery disease in adults, but they also have intrinsic anti-inflammatory properties, which may be especially beneficial in lupus.

[1] Lawrence, R.C., et al. *Arthritis & Rheumatism*, Volume 41, Number 5, May 1998, pages 778 to 799.

5c - GOAL STATEMENT Expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medicines. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs.

Background: Our nation is facing a pressing need for new drugs. Many existing medicines are becoming ineffective due to antibiotic resistance. In other cases, the side effects of existing drugs are as severe as the diseases they are designed to treat. Meanwhile, the number of new drug applications submitted in recent years has dropped precipitously, according to the Food and Drug Administration.[1] Most drugs are discovered by randomly screening thousands of chemical compounds for desired biological effects. To speed the discovery of new medicines, scientists need to have access to larger collections of chemicals to test. An especially promising approach to invigorating and strengthening the new drug pipeline is by using a new and powerful chemical strategy called diversity-oriented synthesis. This method can quickly generate a large number of potential drug compounds (a "chemical library"). Such a library could contain anywhere from a few chemical compounds to millions, and can be designed to include either related versions of a single molecule or a wide variety of completely new chemical structures. This new technique offers unprecedented opportunities for the discovery of molecules that may be developed into lifesaving drugs.

Rationale: Since diversity-oriented synthesis is such a new and intellectually challenging endeavor, the number of methods for designing, making, and analyzing chemical libraries is still limited. This restricts the variety of structures that chemists can make. Although the pharmaceutical industry has embraced chemical library screening as a useful drug discovery strategy, it has not invested in the long-term research needed to improve the technique. Similarly, few academic scientists have made a special effort to develop chemical library-related methods. The investment will likely enrich the field of diversity-oriented synthesis and give pharmaceutical scientists important tools for discovery of molecules that show promise as future medicines.

[1] U.S. Food and Drug Administration (2002). FY 2001 Performance Report to Congress for the Prescription Free Drug User Act of 1992 [Online]. Available: http://www.fda.gov/oc/pdufa/report2001/pdufareport.html

5d - GOAL STATEMENT: By fiscal year 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.

Disease Burden: Diseases of the nervous system–stroke, trauma, drug addiction, alcoholism, autism, unipolar major depression, epilepsy, Parkinson's disease, schizophrenia, multiple sclerosis, chronic pain, and hundreds more–collectively constitute one of the largest disease burdens in terms of disability, costs, personal tragedy, and death.

Rationale*:* Identification of small molecules with promise as drugs, diagnostic agents, and research tools is critical for the development of new or improved treatments for diseases of the nervous system. Recent advances in understanding the nervous system and its disorders at the level of cells and molecules have revealed new targets for drug development, that is steps in the disease process at which a drug might act with a beneficial effect. In addition, the development of cell culture and animal models of human disease has greatly facilitated the testing of potential drugs. We can now evaluate large collections of molecules, which will provide an increasing number of promising candidates for further development as drugs, diagnostic agents, and research tools. Although other exciting approaches are being explored, for the immediate future small molecules will continue to constitute the vast majority of new therapies and tools for treating, diagnosing, and studying disorders of the nervous system.

6a - GOAL STATEMENT: Identify the genes that control the risk for the development of age-related macular degeneration and glaucoma in humans.

Prevalence/Incidence: Age-related macular degeneration is a sight-threatening degenerative eye disease that affects the part of the retina known as the macula and leads to varying degrees of vision loss depending on the form and severity of the disease. Of the nearly 60 million people in the United States age 55 or older in the year 2000[1], approximately eight million are at risk of developing advanced, sight-threatening age-related macular degeneration in one or both eyes within five years.[2] Glaucoma is a group of eye disorders that shares a distinct type of optic nerve damage that can lead to blindness. Approximately 2.2 million Americans have glaucoma[3] and an estimated 2 million more are unaware that they have the disease. As many as 120,000 are blind from this disease.[4]

Disease Burden: Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the United States among persons over 65 years of age, the fastest growing segment of the US population. AMD threatens the eyesight and independence of our growing population of older Americans. People over age 60 are at greatest risk for AMD. Glaucoma is also a major public health problem and the number one cause of blindness in African Americans. It is often described as a silent thief of sight, because there may be no symptoms in the early stages of the disease process until the loss of side or peripheral vision becomes noticeable. As the disease progresses, the field of vision narrows until blindness results. Blacks over age 40, everyone over age 60, and people with a family history of glaucoma are at increased risk for glaucoma.

Rationale: The development of effective treatments for AMD has been limited by the complicated nature of the disease and the fact that the pathophysiology of the disease is poorly understood. The genes for other forms of macular degeneration, including Stargardt disease and Best macular dystrophy, have been identified and are being studied to learn whether similar disease mechanisms are involved in AMD. These genes have also been considered as candidate genes for AMD, but the results suggest a complex underlying genetic predisposition or susceptibility to biological and environmental factors in the pathogenesis of this complex disorder. Further investigation of the genes that control this predisposition or susceptibility may improve our understanding of the disease process and ultimately lead to improved treatments or the means to prevent this disease. Glaucoma is not a single disease but rather a group of diseases characterized by a particular type of retinal ganglion cell death that is usually, but not always, associated with an increase in intraocular pressure. Current treatments, whether surgical or pharmacologic, are aimed at reducing intraocular pressure and are often inadequate in preventing vision loss. A variety of mutations have been identified that may play a role in the development of primary open angle glaucoma. The multiple genetic loci and gene associations linked to various forms of glaucoma are further indication of the complex nature of this disease and underscore the need for additional research to clarify the roles of environmental and genetic risk factors in the pathology of this heterogeneous disease.

[1] U.S. Census: Profile of General Demographic Characteristics: 2000.
[2] AREDS Study Group. A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation With Vitamins C and E, Beta Carotene, and Zinc for Age- Related Macular Degeneration and Vision Loss. *Arch Ophthalmology* 119: 1417-1436, 2001
[3] Prevent Blindness America. Vision Problems in the U.S.: Prevalence of Adult Vision Impairment and Age-Related Eye Diseases In America. 36 pp. (2002)
[4] Health Service. Publication No. (NIH)73-427. pp. 120-143.

6b - GOAL STATEMENT: By 2011, assess the efficacy of at least three new treatment strategies for reducing cardiovascular morbidity/mortality in patients with type 2 diabetes and/or chronic kidney disease.

Prevalence: Prevalence of both diabetes and kidney disease is rising. These diseases markedly increase the risk for life-threatening cardiovascular disease (CVD).

- In 2000, the prevalence of diagnosed diabetes in the U.S. was 7.3%, a 49% increase since 1990.[1] Currently, an estimated 17 million Americans suffer from diabetes; of these, approximately 16 million have type 2 diabetes.[2]
- CVD accounts for two thirds of deaths in people with diabetes.[3]
- Chronic kidney disease affects an estimated 10 to 20 million Americans[4] and can lead to kidney failure.
- The number of patients with kidney failure (ESRD) has doubled over the last decade, and now stands at nearly 400,000.[5]
- Heart disease and stroke are the leading causes of death in patients with ESRD.[6]

Disease Burden: We face national epidemics of both type 2 diabetes and kidney failure. In 1997, the economic cost of diabetes in the U.S. was estimated at $98 billion.[7] Once considered a disease of adults, type 2 diabetes now increasingly strikes during childhood. Rates of type 2 diabetes are approximately twice as high in African American and Hispanic populations as in Caucasian Americans, and are even higher in Native Americans.[2] Among adults with diabetes, heart disease death rates are two to four times higher than in the general population[8]. Diabetes also negates the protection gender affords non-diabetic women.[9] Even among individuals with impaired glucose tolerance, in whom glucose levels are higher than normal but do not yet indicate diabetes, CVD death rates are elevated 1.4 fold.[10] Chronic kidney disease is also a significant health burden. In its most severe forms it leads to kidney failure, also called end-stage renal disease (ESRD), where either dialysis or kidney transplantation is required to maintain life. About one-half of new cases of ESRD have kidney disease as a consequence of diabetes.[11] The number of patients with ESRD has doubled over the last decade, with the increasing disease burden most marked in minority populations, especially African Americans and Native Americans.[5] The markedly reduced life expectancy of patients with end-stage kidney disease is largely due to death from heart disease and stroke; rates of CVD are 10- to 100-fold greater than in the general population.[6] Notably, even among chronic kidney disease patients with a mild to moderate reduction in kidney function, CVD rates are increased two to four fold.[12] The cost of caring for the ESRD population was $19.4 billion dollars in 2000[13] and consumed about 6% of the Medicare budget.[14]

[1] Mokdad et al., 2001. *JAMA* 286: 1195-1200.
[2] National Diabetes Statistics, March 2002, NIH Publication No. 02-3892.
[3] Geiss et al., Mortality in Non-Insulin-Dependent Diabetes. In: *Diabetes in America*. NIH, NIDDK. 1995, pages 233-257.
[4] National Kidney Foundation, 2002*, Am. J. Kidney Dis.* 39: S1-S266 (suppl).
[5] United States Renal Data System 2002 Annual Data Report, NIH, NIDDK, pp. 44-50
[6] United States Renal Data System 2002 Annual Data Report, NIH, NIDDK, p. 167; Sarnak and Levey, 1999, *Seminars in Dialysis* 12: 69-76.
[7] 1998, Diabetes Care 21: 296-309.
[8] Haffner et al., 1998, *N. Eng. J. Med*, 339: 229-34.
[9] Wingard and Barrett-Conner, Heart Disease and Diabetes. In: *Diabetes in America*. NIH, NIDDK. 1995, pages 429-448.
[10] Saydah et al., 2001, Diabetes Care 24: 447-453.
[11] United States Renal Data System 2002 Annual Data Report, NIH, NIDDK, pp. 60-70.
[12] Sarnak and Levey, 2000. *Am. J. Kidney Dis*. 35: S117-31.
[13] United States Renal Data System 2002 Annual Data Report, NIH, NIDDK, p. 18.
[14] Eggers, 2000, *Seminars in Nephrology* 20: 516-522.

Rationale: For both diabetes and kidney disease, premature CVD is the major cause of death. CVD in patients with type 2 diabetes and with kidney disease is associated with some of the same risk factors as in the general population, including obesity, hypertension, and abnormal blood lipid levels, but these diseases confer substantial additional risk for CVD. Recent clinical trials have established the benefit of intensive management of blood pressure and LDL-cholesterol in reducing CVD risk, but a number of potential strategies to reduce the risk of CVD in these conditions require further exploration. While even moderate weight loss can dramatically reduce the development of type 2 diabetes in those at high risk, a benefit of weight loss in preventing cardiovascular complications in people with diabetes has not yet been established. While improved blood glucose control dramatically reduces the eye, kidney, and nerve complications of diabetes, its benefits in reducing CVD are not fully established, nor is it known whether insulin-providing or insulin-sensitizing strategies for glucose control are optimal for reducing CVD. Lowering of LDL cholesterol has been shown to prevent CVD, but type 2 diabetes is associated with a distinct lipid profile, with low HDL cholesterol and increased triglycerides, and research is needed to establish optimal management of lipids and blood pressure to reduce CVD in type 2 diabetes. Homocysteine levels rise as the kidneys fail, and homocysteine has long been known as a risk factor for CVD. Folate and B-vitamin supplementation can normalize homocysteine levels in patients with mild chronic kidney disease. It is not yet clear, however, whether this will reduce the risk of CVD. A major goal of NIH-funded research is to discover and evaluate strategies to reduce risk factors for, and to effectively treat, CVD in patients with diabetes and/or kidney disease. If successful, this research would extend lifespan and improve quality of life.

6c - GOAL STATEMENT: By 2012, develop a knowledge base on Chemical Effects in Biological Systems using a "systems toxicology" or toxicogenomics approach.

Background: Toxicogenomics is a new scientific field that examines how chemical exposures disrupt biological processes at the molecular level. This knowledge could be catalogued in a way that would allow researchers to predict adverse health effects of relatively unstudied chemicals and drugs; they could even predict how individuals would differ in their response to these compounds. Toxicogenomics would accomplish these feats by studying how the basic building blocks of biological systems – our genes – respond to environmental toxicants and other stressors. When a person is exposed to a chemical, cells in the body may respond by switching on (upregulating) some genes and switching off (downregulating) others, potentially changing the proteins that are produced by the cells. The pattern of regulation of various genes is different for different chemicals, creating a characteristic pattern or "signature," which scientists hope will be useful in classifying chemicals and other stressors by their biological activity. This signature pattern would provide a means of predicting effects on human health from chemicals we currently know little about.

Toxicogenomics seeks to use these signature gene expression patterns to go beyond the traditional toxicological tools of testing animals for adverse outcomes that might indicate toxicity. Traditional methods, such as physical examinations, tissue samples, and blood tests, would be replaced with techniques using DNA microarray technology. The power and potential of these new toxicogenomics methods are capable of revolutionizing the field of toxicology. We anticipate that our understanding of mechanisms of toxicity and disease will improve as these new methods are used more extensively and toxicogenomics databases are developed more fully. The result will be the emergence of toxicology as an information science that will enable thorough analysis, iterative modeling, and discovery across biological species and chemical classes.

Rationale: Quicker and safer development of therapeutic drugs and commercially important chemicals would result if there were a better way to predict adverse reactions early in the development process. This goal is one of the possible outcomes of investments now being made in toxicogenomics.

The pharmaceutical industry is greatly interested in this technology because of their need to speed up the process of toxicological assessment of new R & D products. Identifying molecular events that serve as precursors of adverse health outcomes early in the development process would eliminate much of the expense (estimated in the billions of dollars annually) associated with the development of new pharmaceutical products.

NIH aims to create a Chemical Effects in Biological Systems (CEBS) knowledge base. More than a "database," the CEBS knowledge base will contain data on global gene expression, protein expression, metabolite profiles, and associated chemical/stressor induced effects in multiple species. With such information, it will be possible to derive functional pathways and network information based on cross-species homology.

7a - GOAL STATEMENT: By 2005, evaluate 10 commonly used botanicals for inhibition/induction of enzymes that metabolize drugs as a method of identifying potential botanical/drug interactions.

Prevalence/Incidence: The CDC reported that 29 percent of American adults used at least one complementary and alternative medicine (CAM) therapy in the past year, of which nearly ten percent used a botanical product.[1] A separate study reported that 18 percent of individuals taking prescription drugs were concurrently using botanical products, high dose vitamins, or both, estimating that 15 million adults are at risk for interactions between drugs and dietary supplements (a large category that includes botanicals, vitamins, amino acids, and similar products other than drugs).[2]

Disease Burden: Heterogeneous in nature, interactions between botanicals and drugs demonstrate a wide range of effects. Peer-reviewed scientific research literature has documented such events. For example, one study of St. John's wort showed it greatly reduced plasma concentrations of the anti-HIV medication indinavir. Similar phenomena have been demonstrated with the cancer drug irinotecan, the immunosuppresant drug cyclosporine, and certain birth control medications. A study of garlic indicated interaction with saquinavir, another anti-HIV medication. Additional studies have documented the potential for herbal products to interact with anesthetic agents.

Rationale: Although botanical products are widely used in the United States, little or no authoritative information is available on potential botanical-drug interactions to either the consumers or health care providers. Likewise, the systematic evaluation of the potential of botanicals to interact with conventional medications has largely gone unexplored. Botanicals are complex mixtures of naturally occurring chemical compounds, some of which proved sufficiently potent to serve as the basis for many current drugs. It could be expected, then, that botanical products could manifest a broad array of interactions with conventional drugs so as to enhance their activity and evoke greater drug toxicity, or to accelerate their metabolism and impair their therapeutic benefits. Compounds contained in some botanical products have already been proven to interact with drugs by inhibiting or inducing specific hepatic cytochrome P450 enzymes that are critical for drug metabolism and elimination. Of this large enzyme system, two specific enzymes, CYP 3A4 and CYP 2D6, are involved in the metabolism of approximately 80 percent of all marketed drugs, thereby providing a rational starting point from which to examine the potential for botanical-drug interactions.

[1] Ni H, *et al*. Utilization of complementary and alternative medicine by United States adults: results from the 1999 national health information survey. *Med Care* 2002 Apr;40(4):353-8
[2] Eisenberg DM, *et al*. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998 Nov 11; 280(18):1569-75.

7b - GOAL STATEMENT: By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarker(s) (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption.

Prevalence/Incidence: Cancer is the second leading cause of death in the United States. During 2001, an estimated 1,268,000 persons in the United States were diagnosed with cancer, including 198,100 prostate cancers; 192,200 female breast cancers; 169,500 lung cancers; and 135,400 cancers of the colon/rectum.[1] These estimates did not include most skin cancers and new cases of skin cancer are estimated to exceed 1 million per year. One-half of all cases of cancer occur in people aged 65 years and over.[2]

Disease Burden: Our Nation's past investments in cancer research are paying major dividends, for example:

- Americans are increasingly adopting good health habits to reduce their cancer risk.[1]
- Overall, cancer rates are dropping, especially for cancers that are diagnosed prior to metastatic spread.[3]
- Overall, the more than 9 million cancer survivors in America are enjoying a higher quality of life than was possible just a few years ago.[1]
- However, in the face of these significant advances, cancer remains a major public healthcare problem and, with the aging and changing demographics of America, expected increases in numbers of new cancer cases loom as a potential healthcare crisis.[3]
- The incidence rates of certain cancers continue to rise. For example, rates of lung cancer in women, non-Hodgkin's lymphoma, and melanoma are increasing.[1]
- The cost of the cancer epidemic is estimated to be in excess of $180 billion per year and this burden will continue to rise as cancer moves to become the number one killer of Americans in the next few years.[3]
- The rates of both new cases and deaths from cancer vary by cancer site, socioeconomic status, sex, and racial and ethnic group.[1]

***Rationale*:** Recent advances in understanding the molecular basis of cancer, and the associated development of novel molecular technologies in areas such as proteomics, portend a future where cancer can be detected early and preempted before it spreads, perhaps on an individualized basis. For example, nanoscience offers unparalleled opportunities to measure and monitor changes within cells at the level of multiple atoms. Nanoscience researchers are developing "nanospheres" that can be deployed in the body to detect real-time changes in normal cells. These nanoparticles can carry a variety of specially designed, molecular-sized attachments allowing them to act as biosensors that can be programmed to detect malignant changes in normal cells and potentially deliver treatment - without harming healthy cells. Applications of nanotechnology have the potential to shift the paradigm of cancer toward earlier detection and prevention, provide a new platform for eventual high-throughput diagnostics, and, ultimately, real-time monitoring of patients.[4]

[1] *Cancer Progress Report 2001;* NIH Publication No: 02-5045, December 2001. page 18.
[2] Ries, L.A.G, et al. *SEER Cancer Statistics Review, 1973–1996.* Bethesda, MD: National Cancer Institute, 1999.
[3] Edwards BK, et al. Annual Report to the Nation on the Status of Cancer, 1973-1999, Featuring Implications of Age and Aging on the U.S. Cancer Burden, May 15, 2002 (Vol. 94, No. 10, pages 2766-2792), *Cancer*
[4] *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2004.;* NIH Publication No: 03-4373, October 2002, page 69.

7c - GOAL STATEMENT: By 2005, create the next generation map of the human genome, a so called "haplotype map" (HapMap), by identifying the patterns of genetic variation across all human chromosomes.

***Prevalence/Incidence*:** Virtually all diseases have a genetic component. The DNA sequences of any two people are 99.9 percent identical. However, there are at least 10 million DNA sites where people commonly differ and these variations may greatly affect an individual's risk for disease or response to drugs.

Disease Burden: The goal of much genetic research is to find genes that contribute to disease. Finding these genes allows an understanding of the disease process, thus enabling development of methods for disease prevention and treatment. For "single-gene disorders," diseases with a relatively straightforward genetic basis, current methods are often sufficient to find the genes involved. Most people, however, do not have single-gene disorders, but develop common diseases such as diabetes, cancer, stroke, heart disease, psychiatric disorders, arthritis, or asthma, which occur due to interactions of multiple genetic and environmental factors. Strategies that work well for single-gene disorders lack the power to map such multi-gene disorders; thus, relatively little is known about the genetic basis of these common diseases, or of the factors that determine individual risk of disease, clinical course, or response to treatment.

Rationale: By understanding the way in which genetic variations are correlated in DNA "neighborhoods," considerable savings in time, effort, and cost can be achieved in uncovering the hereditary factors in common diseases like diabetes, cancer, and mental illness. Sites in the genome where individuals differ in their DNA spelling by a single letter are called single nucleotide polymorphisms (SNPs). Recent work has shown that about 10 million SNPs are common in human populations. SNPs are not inherited independently; rather, sets of adjacent SNPs are inherited in blocks. The specific pattern of particular SNP spellings in a block is called a haplotype. Although a region of DNA may contain many SNPs, it takes only a few SNPs to uniquely identify or "tag" each of the haplotypes in the region. This presents the possibility of a major shortcut in identifying hereditary factors in disease. Instead of testing 10 million SNPs, a rigorously chosen subset of about 400,000 SNPs could provide all of the essential information.

Most common haplotypes occur in all human populations, although their frequencies may vary considerably. Initial studies also indicate that the boundaries between the blocks are remarkably similar among populations in Europe, Asia, and Africa. These data indicate that a human haplotype map built with samples from these three geographic areas would apply to most populations in the world, although further testing of this conclusion is needed.

The NIH has taken a leadership role in the development of the HapMap, a catalog of the haplotype blocks and the SNPs that tag them. The HapMap will be a tool that can be used by researchers studying many diseases, to find the genes and variants that contribute to those diseases. In addition to its use in studying genetic associations with disease, the HapMap will be a powerful resource for studying the genetic factors contributing to variation in individual response to disease once it does occur, as well as to drugs and vaccines. It will also be a potent tool for better understanding the interactions of genes with environmental factors. Ultimately, the development of this powerful tool will allow the biomedical research community to understand complex genetic diseases much more fully and will lead to improved treatments and, ultimately, cures for many of these disorders.

8a - GOAL STATEMENT: By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases.

Background: Genome sequencing reveals the lineup of paired chemical bases that make up the pathogen's DNA, the language of life. The potential payoffs of sequencing pathogens are enormous. Sequencing information can be exploited in many ways: to identify molecules for vaccine and drug development; to identify mutations that contribute to drug resistance; to compare the genomes of different strains of pathogens and to note differences that may effect the virulence of a microbe or its ability to evoke disease; and to trace microbial evolution. When scientists identify genes that are unique to a particular microbe, drugs can be targeted to these genes, and the products of these genes can be incorporated into experimental vaccines. Furthermore, strategies can be devised to counteract genetic mutations that cause a microbe to become drug resistant. Once genes are found that are associated with infectious disease, researchers can attempt to disable them. Moreover, genetic variations detected in different strains of the same pathogen can be used to study population dynamics of these strains, such as the spread of a virulent form of an organism in a susceptible population. In addition, understanding the genetic basis for both virulence and drug resistance also may help to predict disease prognosis and influence the type and extent of patient care and treatment.

Recognizing the incredible potential of microbial genomics research, the NIH has made a significant investment in the large-scale DNA sequencing of the genomes of human pathogens and invertebrate vectors of disease, including microorganisms considered to be potential agents of bioterrorism. The genome sequences of thirty-two bacterial pathogens, a parasitic protozoa, 1 chromosome of another parasitic protozoa, and an invertebrate vector (an organism that spreads disease, e.g., a mosquito) have been completed with NIH support (http://www.nidr.nih.gov/research/dbts/microbial_lrg_scale_DNA_prjs.asp; http://www.niaid.nih.gov/dmid/genomes) and these sequences have been released rapidly to the scientific community through a publicly accessible web site. NIH has funded projects to sequence the full genomes of a number of medically important microbes, including the bacteria that cause tuberculosis, gonorrhea, chlamydia, cholera, strep throat, scarlet fever, and foodborne diseases. Recently, the complete genome sequences of *Plasmodium falciparum* and *Anopheles gambiae*, the most lethal malaria-causing parasite and its mosquito vector, respectively, were published, providing a valuable resource to the scientific community. This work, which was supported in part by NIH, will provide the basis for further experimental studies to understand the pathogenesis of the parasite and its vector, and provides potential molecules that could serve as the basis for the next generation of drugs, vaccines, and diagnostics.

Rationale: Significant progress in DNA sequencing technology has allowed genomic DNA to be sequenced more efficiently and cost-effectively. In fact, it is now possible to sequence a bacterial genome in a month or less. DNA sequencing technology is being improved further, and innovative new sequencing technologies that will revolutionize the speed, efficiency and cost by several orders of magnitude are in the immediate future. A critical companion to state-of-the-art DNA sequencing techniques are the bioinformatics, computational tools and databases that provide the scientific community with the needed resources to query, analyze and annotate the sequencing data, and assemble genomes.

8b - GOAL STATEMENT: Identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals.

***Background*:** Both skeletal health and the maintenance of normal blood calcium levels depend upon the process of bone turnover, in which small regions of bone are broken down (resorbed) and then replaced with new bone. The regulation of the balance between bone resorption and new bone formation, which can be affected by nutritional, endocrine, and pharmacological factors, is critical to maintaining bone mass and preventing fracture. An excess of resorption over formation underlies many bone diseases, such as post-menopausal osteoporosis.

Osteoblasts are the cells that form new bone during bone turnover. In addition, some osteoblasts remain embedded in the bone, becoming osteocytes. Recent work has shown that osteocyte survival is an important requirement for skeletal health. Bone itself is composed of mineral crystals embedded in a matrix made up of many different proteins. There is evidence that interactions between matrix proteins and proteins found at the cell surfaces of osteoblasts and osteocytes produce signals that are important for the regulation of bone turnover and the survival of osteocytes. However, the molecular details of cell-matrix interactions have been explored in only a few instances. If known, the mechanisms of these interactions could yield targets for new drugs that might act to stimulate bone formation or block bone resorption.

Rationale: Recent advances, particularly in the genetic manipulation of mice, make it possible to define the function of different matrix proteins and the cell surface proteins that interact with them. For example, mice can be created that either lack a certain matrix protein or produce abnormally large amounts of the protein. Cell surface proteins thought to interact with matrix proteins can also be tested in this way. It is important to conduct these experiments with intact, genetically modified mice, rather than in cell culture, for two reasons. First, although osteoblasts can be induced to produce bone matrix in culture, the interaction between cells and matrix in culture is not normal. For example, osteoblasts do not become osteocytes within the bone produced in culture. Second, the consequences of interfering with specific cell-matrix interactions can be assessed thoroughly by examining the bones of mice. This can even indicate the ultimate effect on the mechanical strength of the bones.

It is clear from work to date that altering cell-matrix interactions can produce changes in bone remodeling activity and bone mass. However, in order to accelerate progress toward this goal, we need to refine our understanding of known cell-matrix interactions, and identify new interactions with important roles in the maintenance of skeletal health.

8c - GOAL STATEMENT: Build a publicly accessible Collection of Reference Sequences to serve as the basis for medical, functional, and diversity studies. A comprehensive Reference Sequence Collection will serve as a foundation for genomic research by providing a centralized, integrated, non-redundant set of sequences, including genomic DNA , transcript (RNA), and proteome (protein product) sequences, integrated with other vital information for all major research organisms.

Background: The Reference Sequence Collection will provide a unified view of our genetic knowledge of organisms. A single, high-quality collection of reference sequences for multiple species that is richly annotated and highly connected to other information sources will make it possible to undertake large-scale comparative analyses. The ability to make discoveries in one organism (such as mouse models of a human disease) and immediately apply them to another organism (such as humans) is one of the most powerful aspects of molecular biology. The academic and pharmaceutical research communities use reference sequences in this way to investigate basic molecular biological processes and medical problems, such as different disease susceptibilities for individuals or targeted individual drug treatment approaches. The availability of a Reference Sequence Collection means that time once spent identifying resources, gathering data, and reviewing its quality is freed for research.

Rationale: Hundreds of millions of dollars have been invested by Federal agencies, international governments, and charitable foundations to obtain genomic and transcript sequence data for organisms from human to viruses. Although a wealth of sequence data is now available, it exists in multiple formats and locations and is not connected to other information; furthermore, the data produced by different groups are often redundant, inconsistent, or partially overlapping. Without a cohesive representation of the data, it is difficult to reap the full benefit of the massive public investment in obtaining the data. The Reference Sequence Collection will serve as a foundation for genomic research by providing a centralized sequence set integrated with other information including publications, phenotypes, and disease catalogs. This collection must be built and maintained through both computational and expert analysis in order to integrate large quantities of disparate data while also providing a high-quality resource. Both the computational and expert tasks must be ongoing so that: 1) the collection stays current as new data become available; 2) quality is ensured; and 3) new opportunities that add value are identified.

8d - GOAL STATEMENT: By 2009, assess the impact of two major Institutional Development Award (IDeA) programs on the development of competitive investigators and their capacities to compete for NIH research funding.

***Background*:** The IDeA program was authorized within the NIH Revitalization Act of 1993. State eligibility is based on the aggregate level of NIH grant funds received by research institutions collectively within a state over the preceding 5 consecutive years and the average success rate of research applications over that same time span. Between 1997-2001, states that received less than $75 million in NIH grant awards and/or held a success rate of less than 20 percent over than time span, qualified for the IDeA program. The 23 IDeA eligible states include Alaska, Arkansas, Delaware, Hawaii, Idaho, Kansas, Kentucky, Louisiana, Maine, Mississippi, Montana, Nebraska, Nevada, New Hampshire, New Mexico, North Dakota, Oklahoma, Rhode Island, South Carolina, South Dakota, Vermont, West Virginia, and Wyoming as well as Puerto Rico.

The IDeA program is intended to develop the research infrastructure and competitiveness of faculty among institutions located in states that historically have not fully participated in NIH research programs. Although the program was first established in FY 1993, the limited budgets had precluded development of major programs. However, as the appropriation for the IDeA program has become more robust in recent years, the IDeA program has been restructured and further enhanced. The funding level of the program has increased from $750,000 in FY 1993 to $160 million in FY 2002.

Investigators in IDeA states earned a significant increase of NIH awards between 1997 and 2002. In 1997, investigators received 477 NIH research project grant awards and 679 in FY 2002, a 42.3 percent increase. Over that same time span, the number of applications submitted by IDeA state investigators increased from 2355 to 2744, a 16.5 percent increase. The appropriation for the IDeA program increased from $750,000 in FY 1993 to $10 million in FY 1999. In FY 2000, the program increased to $38.5 million, which allowed the design of the first major IDeA program and its implementation.

The new program, Centers of Biomedical Research Excellence (COBRE), was specifically designed to enhance the pool of well-trained investigators who could successfully compete for NIH grant awards. The COBRE program augments and strengthens institutional biomedical research capacities by expanding or modifying research facilities, equipping laboratories with modern research equipment and providing support for developing research faculty through support of a multi-disciplinary center, led by a peer-reviewed, NIH-funded magnet investigator.

In FY 2001, the IDeA program increased to $100 million, which allowed the IDeA program to add another program, the Biomedical Research Infrastructure Network (BRIN). BRIN is intended to enhance the caliber of scientific faculty at undergraduate schools, which will, in turn, attract more promising students to those institutions.

Rationale: Strong congressional interest in IDeA, along with significant increases in funding of IDeA programs, have led to questions about whether programs designed to enhance competitiveness of investigators have led to more NIH research grants to more investigators. The planned study will assess the impact of the IDeA programs on NIH research funding, as a percent of total NIH funding among the cohort of eligible states, and determine the factors that have had the greatest impact on enhancing investigator competitiveness.

9a - GOAL STATEMENT: By 2010, demonstrate through research a capacity to reduce the total years lost to disability (YLDs) in the U.S. by 10 percent by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences at least two comorbid physical illnesses (e.g., heart disease, cancer, Parkinson's disease or diabetes). Major depression is now the leading cause of YLDs in the Nation.

Prevalence/Incidence: Depressive disorders are serious medical illnesses that affect more than 20 million Americans ages 18 and older and an estimated 4-5% of children and adolescents.

- ~9.9 million adults (5%) have major depressive disorder (MDD) [1]
- ~10.4 million adults (5.4%) have dysthymia, a moderate but chronic form of depression; an estimated 40% people with dysthymia meet criteria for MDD or bipolar disorder (BP) in a given year.[1]

The failure of depressed patients to respond satisfactorily to an adequate clinical trial of antidepressant medication or psychotherapy (an estimated 50%), and the frequency with which patients are left with unresolved symptoms or impairments (an estimated 20%) are important issues because residual symptoms are associated with significant functional impairment and substantially increase the risk of relapse and recurrence. Estimates from clinical populations indicate that patients with major depression will experience an average of four lifetime episodes of 20 weeks each in duration, but risk may vary by the number of prior depressive episodes. Those with at least three prior episodes show 70-80% relapse rates, compared to those with no depression history who show 20-30% relapse rates.[2]

Disease Burden: Depressive disorders are prevalent, disabling, often chronic, and potentially fatal illnesses; about 60% of people who die by suicide have had a mood disorder (e.g., major depression, bipolar disorder, dysthymia).[3] The WHO *World Health Report – 2001* identifies major depressive disorder as the leading cause of Disability-Adjusted Life Years (DALYs), i.e., the composite of Years Lost to Disability (YLDs) and potential Years of Life Lost (YLLs) to premature death, in the U.S.[4] Depression accounts for 2.6% of total DALYs among men, and 6.77% among women.[5]

Mediated through the brain, mood disorders disrupt every facet of a person's life: emotions, thought processes, behavior, and physical health. In addition to the inherent effects of depression on health through sleep and appetite dysregulation, self-medicating substance abuse, and physiologic disturbances (e.g., sticky platelets) that are just beginning to be understood, major depression can influence significantly the outcome of comorbid general medical illnesses. Depression is seen frequently in people with coronary heart disease (CHD) and other cardiac illnesses; for example, among patients with congestive heart failure, estimates of the prevalence of major depression range from 17- to 37%. Untreated depression increases the risk by as much as six-fold of dying from heart disease. People with comorbid diabetes and depression have an eight times greater relapse rate than those with depression but without other medical conditions. The prevalence of major depression in patients after a stroke is approximately 20%, and estimates of lifetime rates of depression among persons living with HIV range from 22 to 45 percent. [6]

Rationale: Efficacious and effective treatments benefit millions of persons with major depression; however, a significant proportion (~25-33%) of persons with depression are not helped or do not fully

[1] The Numbers Count: Mental Disorders in America. NIH Publication No. 01-4584
[2] Judd L (1997) The clinical course of unipolar major depressive disorders. *Arch Gen Psychiatry* 54:989-991.
[3] Conwell Y, Brent D (1995). Suicide and aging. I: Patterns of psychiatric diagnosis. *Int Psychogeriatr* (2):149-64.
[4] WHO: The World Health Report 2001. Mental Health: New Understanding, New Hope. WHO, 2001
[5] Michaud CM, et al. (2001), Burden of Disease: Implications for Research. *JAMA* 285:535-539.
[6] The Strategic Plan for Mood Disorders Research of the National Institute of Mental Health. NIH Publication No. 02-5121.

recover when given a standard pharmacological or psychosocial intervention, or depression is not recognized in the context of other general medical illnesses. In pursuit of this goal's focus on treatment resistant depression, NIH will assess effective pharmaceutical algorithmic approaches as well as study how to improve clinicians' capacities for timely identification of patients who have unrecognized or refractory depression. With respect to the goal's focus on reducing the recurrence of depression, NIH will continue to encourage new treatments that build in relapse/ recurrence components to initial treatment approaches. With regard to the focus on depression comorbid with general medical illnesses, NIH will seek to develop (a) fundamentally new clinical interventions and (b) algorithms for the informed use of existing treatments in the face of treatment resistance. Similarly, NIH will target research on identifying biological, behavioral, psychosocial, cultural, and environmental risk and protective factors linking mental and medical disorders. The aim of these studies will be to ascertain those factors that account for the greatest relative variance in the prevalence of depression-comorbid illness and those that are modifiable. The premise of this goal is that targeted research on these topics will have a disproportionate impact on the overall reduction of YLDs associated with depression.

9b - GOAL STATEMENT: By FY 2010, identify culturally appropriate, effective stroke prevention programs for nation-wide implementation in minority communities.

Disease Burden: Although stroke remains the third cause of mortality in the United States and the leading cause of adult disability, the burden of stroke is greater among minority racial/ethnic groups by virtual of its higher incidence and mortality in these populations. The incidence of ischemic and hemorrhagic stroke is disproportionately high in the African American population, occurs at younger ages, and these disparities may be increasing.[1,2] Mortality from stroke among African Americans is nearly twice that of Caucasian Americans.[3] Moreover, among several minority racial/ethnic groups (including African, Hispanic and Native Americans), the disparity in stroke mortality (both ischemic and hemorrhagic) is especially evident among younger individuals – those aged 45-64 years.[3] However, the burden may be even greater than the stroke incidence and mortality rates indicate. Initial evidence suggests that African Americans may experience more severe strokes and greater residual physical deficits, although these deficits may not be fully reflected by impairment in ability to perform activities of daily living.[4-6] It remains to be determined if other minority racial/ethnic groups also experience more severe and disabling strokes than Caucasians.

Rationale: There is a wide range of hypothesized causes of the excess stroke mortality in the Southeastern U.S. (the "Stroke Belt") and among African Americans. The prevalence of stroke risk factors and the potential impact of reducing those factors vary among racial/ethnic groups, with potentially greater impact associated with reduction or elimination for minorities.[7] Patterns of accessing the existing health care system for acute stroke also vary among racial/ethnic groups; for example, minorities are less likely to use the emergency medical system when experiencing a stroke.[8] The reasons for these racial/ethnic variations in stroke-related risk factors and utilization of health care are not fully understood, but will need to be in order to identify the most effective stroke prevention and treatment programs for minority communities. Prevention programs are a preferred strategy for reducing or eliminating the observed racial/ethnic disparities in stroke, and include both primary and secondary prevention approaches. Primary prevention programs target stroke risk factors to reduce the occurrence of stroke. Secondary prevention programs seek to improve access to timely acute stroke care, thereby reducing mortality and morbidity, and target the use of interventions to prevent subsequent stroke in stroke survivors.

The HHS Research Coordination Council (RCC) has identified "Understanding Health Disparities – Closing the Gaps" as a priority for FY2004, and in its stated priority areas has recognized to need to understand factors contributing to disparities in the development of diseases, injuries, and disabilities; to improve detection and diagnosis of diseases that contribute to health disparities, such as stroke; to improve approaches to delay onset or prevent diseases, injuries, and disabilities that contribute to health disparities; to improve treatments for diseases and disabilities that contribute to health disparities; to expand research using bioinformatics and genomics, including pharmacogenomics, in addressing health disparities; and to enhance research on the intersection between non-genetic and genetic factors in health disparities.

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